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WITNESS my hand this
Twenty-eighth day of April 2003

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AUSTRALIA

PATENTS ACT 1990

PROVISIONAL SPECIFICATION

FOR THE INVENTION ENTITLED:-

"MULTI-ELEMENT SCREENING OF TRACE ELEMENTS"

The invention is described in the following statement:-

Technical Field

The present invention is concerned with methods and devices for sample collection and simultaneous detection and/or quantitation of multiple trace elements in fluid samples.

Background Art

A wide range of trace metals and other elements is necessary for good health and physical well being in humans and other animals; deficiencies in essential elements have been shown to cause general malaise and lead to the induction of specific disease, commonly resulting in death. For many essential trace elements, it is not simply the absolute concentration, but also the inter-element balances that have a profound effect on health. For example, selenium deficiency is implicated in the aetiology of Iodine Deficiency Disorders amongst humans, whilst copper deficiency, associated with high levels of manganese, may be implicated as a predisposing or causative factor in induction of Bovine Spongiform Encephalopathy (BSE) in cattle and, by association, New Variant Creutzfeldt-Jakob Disease (nvCJD) in humans.

Dietary forages, vegetables, grains and fruits, which fix available trace elements as metal colloids within their tissue, have long been regarded as sources of essential trace elements. Such plant-based metal colloids are about ninety-eight percent absorbed and communities and animals that have a balanced range of plant products as essential components of diet may reasonably be expected to display markedly reduced incidence of specific trace element deficiency-related disease when compared with other groups lacking quality forage or a regular vegetable, fruit and grain intake.

The trace element content of vegetative material is directly related to the bioavailability of essential nutrients in soils supporting the vegetation. Soils vary in their trace element content from enriched to impoverished, according to local geology, soil degradation and nutrient impoverishment and as a function of inappropriate cropping practice, which is widespread throughout the world. In addition, soils throughout the world are sustaining increasing anthropogenic chemical damage threatening the existence of many plants and animals. Consequently, human health is being threatened through the food chain.

While the productivity of the soils may be maintained through the application of N-P-K fertilisers, food crops growing on these soils becomes, without the regular application of biologically-available 'balanced' trace elements, progressively impoverished in essential trace elements and minerals. If not corrected, this may result in sharply increased incidences of mineral deficiency-related disease.

Elements may be classified as being essential or toxic to human and animal health. In the case of animals, trace metal deficiency and/or toxicity is due largely to concentration levels controlled by environmental factors, whereas for humans, both environmental and occupational factors may be important; toxic response may a function of both natural and/or anthropogenic influences.

Ignoring carbon, hydrogen and oxygen, the biologically essential major elements are calcium, chlorine, magnesium, phosphorous, potassium, sodium, nitrogen and sulphur. Essential trace elements include bromine, chromium, cobalt, copper, fluorine, iodine, iron, manganese, molybdenum, selenium, silicon and zinc. If bio-available, many of these essential trace elements induce toxic responses, at elevated levels, or if out of balance with synergistic and/or antagonistic elements. Several other elements (lithium, scandium, rubidium, lanthanum) are minor essential elements.

In addition to dietary trace metal deficiency-induced disease, other cohorts of individuals are occupationally or environmentally exposed to a range of toxic element pollutants, which similarly induce general malaise and/or specific clinical symptoms commonly resulting in complications and death. Notable amongst these are arsenic, lead and mercury, which constitute the top three most hazardous substances on the US Environmental Protection Agency's Toxic Substances and Disease Registry priority list.

The leaching of heavy metals into the aquatic environment, and uptake by wildlife in the food chain, may have a profound impact on human health. Cadmium and mercury, in particular, are strongly bio-accumulated in fish and shellfish.

Although it is not possible to quantify the hazards and deleterious effects associated with all trace elements, some elements clearly present a more serious problem than others. Respectively ranked 1, 2, 3 and 7 on the NPL, arsenic, lead, mercury and cadmium, as elemental pollutants, are considered extremely toxic and the health effects of these elements have received a great deal of attention from research workers. Other elements on the list, in alphabetical order, are aluminium, antimony, barium, beryllium, chromium, cobalt, copper, manganese, nickel, plutonium, radium, selenium, silver, thallium, thorium, tin, uranium, vanadium and zinc

Unlike many essential trace elements, the concept of a therapeutic index cannot be applied to toxic elements such as lead, cadmium, mercury and arsenic. These toxic elements play no known role in metabolism, as no enzyme has been identified which specifically requires any of them as cofactors. They are extremely hazardous to life and, resulting from ingestion, have been involved in historic poisoning episodes of both human and animal populations. They are increasing in concentration in both aquatic and

terrestrial environments due to anthropogenic inputs, and thus will continue to be a concern to toxicologists and clinicians.

Hence, proactive intervention to identify trace metal and element aberrations within general populations, thereby enabling the early implementation of targeted remedial strategies with consequent minimization of the huge social impact of trace metal-induced disease, is essential. However, mass screening of general populations for trace metal deficiencies and/or toxic metal excesses, with reference to age, sex, socio-economic status and physical geography, while acknowledged as being highly desirable in terms of preventative medicine, is presently impractical. So too, is the mass screening of human food chain components, such as slaughter animals, prior to their entering the food chain.

Present test methodologies require relatively large volumes of fluid samples (for example, 5-10 ml of blood) and are commonly trace element specific, that is, simultaneous measurement of other trace elements potentially present is not possible. Because of this, other relevant trace metals are either overlooked or require further fluid samples for their determination. In the case of blood, this involves invasive, often traumatic extraction, particularly for young children, babies and the elderly, using hypodermic syringes. The derivative body fluid products require stabilisation and preservation, and having regard for transmissible disease such as HIV, appropriate biohazard handling and disposal. Further, the large volumes required give rise to handling and storage problems.

There is no current technology available that can conveniently be used for the collection and broad-spectrum analysis of the trace element content of large numbers of blood and other body fluid samples. Presently available testing methods are cumbersome and expensive, placing the service outside the reach of the general population, particularly in underdeveloped regions where problems are often greatest.

There is therefore a need for improved methodologies which will enable more efficient and cost effective screening of trace elements in fluid samples.

It is an object of the present invention to alleviate at least some of the disadvantages of prior art methods, or to provide a useful alternative.

Summary of the Invention

According to one aspect of the present invention there is provided a sample collection device comprising an inert collection matrix capable of adsorbing a fluid sample, and a solid support, wherein the inert matrix is affixed to an area of the solid support.

The device of the present invention may also comprise an integral lancing member, capable of piercing for example skin or tissue, to aid in the collection and application of a blood or body fluid sample to the inert matrix. The lancing member may

be mounted adjacent to, within or below the area of inert matrix. There may be included a guiding channel in the inert matrix, to guide the lance should it be disposed below the inert matrix area.

The device may also be equipped with a laser-scannable bar code which may contain patient information or other information concerning the sample, its nature and source. The device may also include an antibiotic barrier, to prevent contamination of the sample to analytical equipment and personnel.

Preferably the inert matrix is applied to only one side of the support. It is also preferred that the area to which the matrix is applied is smaller than the area of the solid support and that it be in the shape of a small tablet-sized disc.

The inert matrix may include hydrophobic and/or hydrophilic components, depending on the nature of the sample and the analysis to be performed.

Preferably the solid support is made of flexible material having sufficient durability to withstand transport and handling. Of course it will be understood that the support can be made of rigid material, depending on the nature of application. It is also preferred that the device is of sufficiently small size to allow transport of the device through mail and for ease of storage. The device may have an integral or separate cover sheath, to protect the inert matrix and prevent possible contamination after collection. The cover sheath also protects the device during transport and handling.

In another embodiment of the invention the sample collection device is of multi-layer construction wherein the collection matrix layer is sandwiched between two supporting layers, on of the supporting layers having an opening which exposes and area of the collection matrix.

The preferred fluid sample is a sample of whole blood, however, separated blood (eg. plasma or serum) and other body fluids can also be used with the same device.

According to another aspect of the present invention there is provided a method of detecting simultaneously a plurality of elements in a fluid sample adsorbed onto an inert collection matrix, comprising:

(i) exposing the sample to high energy radiation capable of ionising at least a portion of the sample, and

(ii) detecting plurality of elements in the ionised portion of the sample by mass spectrometry.

According to a further aspect of the present invention there is provided a method of quantifying simultaneously a plurality of elements in a fluid sample adsorbed onto an inert collection matrix, comprising:

(i) exposing the sample to high energy radiation capable of ionising at least a portion of the sample;

(ii) measuring quantity of a plurality of elements in the ionised portion of the sample by mass spectrometry;

(iii) measuring quantity of ionised portion of sample, and

(iv) determining quantity of the plurality of elements in the sample.

According to another aspect of the present invention there is provided a method of quantifying simultaneously a plurality of elements in a fluid sample adsorbed onto an inert collection matrix having an internal standard applied thereto, comprising:

(i) exposing the sample to high energy radiation capable of ionising at least a portion of the sample and a portion of said internal standard;

(ii) measuring quantity of a plurality of elements in the ionised portion of the sample by mass spectrometry;

(iii) measuring quantity of ionised internal standard in the ionised portion of the sample by mass spectrometry, and

(iv) determining quantity of the plurality of elements in the sample.

According to yet another aspect of the present invention there is provided a method of quantifying simultaneously a plurality of elements in a fluid sample adsorbed onto an inert collection matrix, comprising:

(i) introducing into the fluid sample a known quantity of a measurable internal standard

(ii) exposing the sample to high energy radiation capable of ionising at least a portion of the sample and the internal standard;

(iii) measuring quantity of a plurality of elements in the ionised portion of the sample by mass spectrometry;

(iv) measuring quantity of ionised internal standard in the ionised portion of the sample by mass spectrometry, and

(v) determining quantity of the plurality of elements in the sample.

Preferably, the sample is whole blood and sample size is approximately 50 to 100 µl and even more preferred size of sample is 50 µl or less. Of course, separated blood may also be used, eg. plasma or serum.

Also preferred is that the high energy radiation is UV laser radiation and that the sample is exposed to such radiation for a period of approximately 30 seconds.

The preferred elements to be detected and/or quantified are dietary trace elements. Also preferred is detection/quantification of toxic elements in a variety of biological fluid samples.

Description of the Preferred Embodiment

The present invention is in part based on Laser Ablation-Inductively Coupled Plasma-Mass Spectrometry technique, which allows rapid, automated, cost effective mass screening of general populations, bloodstock, zoo animals, pets and slaughter animals to identify trace element aberrations in body fluids. This technology facilitates proactive remedial intervention to target and correct essential trace element imbalances and/or toxic heavy metal excesses and enables identification and rejection of heavy metal-contaminated slaughter animals designed for human consumption.

The present invention in its various embodiments allows the simultaneous analysis of a broad spectrum of trace elements (some fifty elements), at a cost lower than that of a large number of single element analyses currently being performed, on an chemically unmodified 50-100 micro-litre volume of body fluid sample (single drop) adsorbed onto an inert collection matrix. The sample collection device, and collection protocol, eliminates the use of hypodermic syringes, and hence potential for stick injuries, is non-invasive and hence, non-traumatic, and does not involve the preservation, movement and storage of large volumes of blood and urine, or involve large biohazard disposal facilities. Indeed, in the case of humans, samples may generally be self-acquired at any geographic location through adsorption of a drop of biological fluid, such as blood from a pin prick, onto a lightweight collection device as described herein, and dispatched to the nearest analytical facility by post or courier. Because an approximately 8000°C argon plasma is involved in ionisation of the samples, the body fluid samples are expected to be largely sterilized during analysis.

Certain embodiments of the present invention have been developed using an ultraviolet laser and quadrupole inductively coupled plasma-mass spectrometer (LA-ICP-MS) with manual sample handling. However, the present methods are equally applicable to Time-of-Flight (ToF) mass spectrometry techniques. Further, the methods of the present invention, whether they make use of quadrupole or ToF mass spectrometry, can be automated to allow rapid, high volume throughput screening of samples.

The methods and devices of the present invention permit cost effective, simultaneous, automated mass screening of blood, and other body fluids, for a wide range of essential and toxic trace elements on micro-liter volumes of test fluid absorbed onto inert collection matrices. In certain preferred embodiments the core of the analytical system comprises a Time of Flight Laser Ablation-Inductively Coupled Plasma-Mass Spectrometer with associated automated sample insertion system.

The invention will now be described in more detail with reference to non-limiting examples.

Examples

Example 1: Sample Collection Device

The sample collection device of the present invention incorporates an inert fluid absorption matrix, typically shaped in the form of a small tablet-size disc. The matrix is encased in a small, lightweight, disposable or re-cyclable holder (disc holder or solid support material). Ideally the holder is made of relatively rigid material (for example plastic, cardboard or similar material). The device is designed so that a drop of blood or body fluid can be placed on the absorption matrix and the device sealed at the site of collection. Thus immobilized sample can be easily transported via post or courier to a sample analysis center and/or stored.

A preferred collection device of the present invention, incorporating a number of features described below, is depicted in Figure 1. In plan view (A) the device is typically rectangular in shape and has an area of absorbent collection matrix (1) disposed on the surface, and may also have a bar code (2) containing relevant information about the sample and/or the subject. The collection area shown is circular in shape but may be any other suitable shape. A cover sheath (B) may be provided, to cover the collecting matrix area after the sample has been collected. Figures 2 and 3 show the collection device in cross section, in closed and open positions respectively. The carrier or backing portion (A) of the device can be suitably made of plastic or some form of card (stiff paper, cardboard and the like) material. The cover sheath (B) may be made of similar materials. Both the backing portion and the cover sheath may include a locking ridge (3), for positive engagement between the backing and cover sheath, and also to prevent the cover sheath, if used, from sliding off entirely.

Figures 2 and 3 also show the area of collection matrix (1) and a stylus or lance (5) disposed below the collection matrix and within the carrier or backing material. The lance may be guided by a channel (4) in the collection matrix, so that when the device is pressed between the thumb and a finger, the lance will be forced through the channel and into the finger, thus piercing the finger and enabling a sample of blood to be collected onto the collecting matrix. Once the sample has been taken, the cover or sheath can be slid over the collecting matrix, thus protecting the sample as well as individuals handling the used device.

Figure 4 is an enlargement of a section of figures 2 and 3, showing in more detail the preferred arrangement of the lance, collection matrix and the guiding channel.

Typically, a collection device contemplated herein, in a particular preferred configuration will have dimensions of approximately 40x20 mm and will be about 2 mm

thick. However, larger or smaller collection devices may be useful in different applications and can be designed along equivalent parameters.

The collection device is primarily designed for the collection of blood and other body fluids prior to analysis of the trace element content. However, similar design principles can be used for sample collection of other fluids.

The design of the sample collection device provides for low manufacturing costs, a robust configuration, ease of transportation, ease of storage, and can be used to collect a drop of test sample from a remote site by an inexperienced collector.

The matrix, which forms an integral part of the device, is typically an inert material with respect to fluid interaction prior to analysis and does not interfere with the subsequent sample analysis. The sample adsorbed onto the matrix can be stored indefinitely, without the addition of preservatives that may add contaminants to the sample.

The matrix should have optimal thermal absorption and heat dissipation qualities for any particular application and hence, a single type of matrix may not be optimal for all types of body fluids. However, simple trial and error will determine the suitability of a matrix to a particular application.

The collection device relies on the use of hydrophobic and hydrophilic layers to ensure correct sampling and immobilization of the blood or other body fluid, without producing a chromatographic effect. These layers may employ inorganic and/or organic components.

The inorganic materials suitable for a matrix of the ceramic-type are compounds of lithium, boron, carbon, magnesium, aluminium and silicon. Although this list is not exhaustive, it does encompass the main ingredients for an appropriate robust thermo-ceramic. Other suitable materials will be known to those skilled in the art. Furthermore, the absorbing matrix should have suitable thermal and cohesive properties. If desired, organic components can then be incorporated as required.

Typically, a sample of blood is transferred to the collection device that has a small lance or puncturing needle incorporated into the matrix, or into the backing/support material. The patient grips the device and causes a small pinprick to be administered. The collected blood does not have to have a specific volume as the matrix can be encoded with an internal standard, which normalizes the analytical data on analysis.

The device can have a laser-scannable bar code for recognition of the patient or to include any other additional information on the sample and its source. The amount of blood required is usually less than 50μL. The device can also have a sealing mechanism to ensure that the device plus sample can be transported and will not be contaminated.

The matrix may be affixed to the support material or holder by any known means and may employ adhesives. Further, an antibiotic barrier may be applied to prevent contamination of the sample or the analytical equipment and personnel.

The preferred support medium is one that is inert, refractory and capable of UV-laser coupling with a high fluence. Typically, it contains levels of contaminants that are significantly lower than those expected in biological systems. It may consist of both hydrophobic and hydrophilic components to better control the absorption of fluid media. The blood sampling mechanism is typically by capillary spread of fluid through the absorbing matrix. Segregation of components through chromatographic influence can be minimized through the control of the migration process.

Example 2: Sample Analysis System

Traditionally, quantitation in LA-ICP-MS has been approached by controlling the power coupling the laser to the sample, to ensure uniform ablation characteristics and transfer of uniform amounts of solid to the analytical plasma. While this has much to recommend it when the nature of the matrix can be assured (eg. glass or similar), there are significant problems associated with standardisation of the coupling and transfer efficiency when matrices are not uniform. Furthermore, when the surface characteristics of the sample also vary it is extremely difficult to ensure uniform ablation.

Until the present invention laser ablation ICP-MS technology has been at best a semi-quantitative technique and more usually a comparative technique for the determination of trace element levels in any solid material. In this embodiment of the invention quantitation in LA-ICP-MS has been approached by quantitation of the amount of debris (ablated or ionised material) that is actually transported from the laser cell to the analytical plasma.

When using an Infrared laser, where the particle size of ablated material is relatively large, Ultra-violet spectral interference can be used to quantify the amount of particles (ablation efficiency) entering the plasma. However, in the majority of cases the techniques currently employ either UV or Excimer lasers. These lasers produce particles that are too small to have sensible UV scattering and consequently relatively inexpensive particle quantitation is not possible. However, laser interferometry can be used, as an appropriate alternative technique, to quantitate the amount of ablated material and thus the efficiency of UV lasers. Once transport efficiency is quantified, it is then possible to quantify the amount of particles that are entering the analytical plasma and hence quantify the resulting signal (ie. amount of any one element).

The quantification process can be further enhanced by using internal standards in the support matrix of the collection/transportation device described above. A suitable

internal standard can be selected from elements which are not commonly present or are below detectable levels in a particular sample. Thus, for blood samples, elements such as Hf, Ir, Ru, Rh, Ta and heavy rare earths can be used as internal standards, and incorporated into the inert matrix by bonding to the surface of the micro-spherules used to produce the matrix, or may even be present as a natural constituent of the sample itself.

In case where the internal standard is incorporated into the matrix, when the sample is ablated, the spherules of the matrix are carried into the analytical plasma along with the sample. Quantitation of the transport efficiency of all debris is achieved using laser interferometry, or an appropriate alternative technique, and supported by normalisation to the signal from internal standards. Since the bonding characteristics of the internal standards and the efficiency of absorption of the matrix are known, as is the transport efficiency, it is possible to calculate the concentration of the element in the sample adsorbed onto the matrix, in this case blood.

Thus, the LA-ICP-MS has been transformed from a semi-quantitative to a quantitative technique.

The core components of the Sample Analysis System comprise a laser for producing an aerosol of the sample (Laser Ablation), an argon plasma, or 'electrical flame', operating at temperatures in excess of 7,000°C (Inductively Coupled Plasma) in which the aerosol is ionized, a mass filter (Mass Spectrometer) for separating the ions into 'packets' according to their mass to charge ratio, and an ion detector (Multi-channel Analyzer or Ion Multiplier) for detecting the ions in each 'packet'. The entire atomic mass spectrum can be sequentially scanned at rates of approximately 20,000 Hz. The system will operate with a routine sensitivity capable of achieving parts per billion detection limits. All data can be electronically stored for future reference.

ICP-MS systems currently in use utilize a quadrupole mass filter, controlled by alternating RF and DC fields in the quadrupole, to allow transmission of ions of one selected mass to charge ratio at any specific time. Cycling of the quadrupole allows passage of any selected ion with a mass to charge ratio of <250amu at specific times during the cycling program. Each naturally occurring element has a unique and simple pattern of nearly integer mass to charge ratio, corresponding to its stable isotopes, thereby facilitating identification of the elemental composition of the sample being analyzed. The number of registered element ions from a specific sample is proportional to the concentration of the element isotope in the sample.

For multi-element analysis, the quadrupole is generally configured to scan at 1Hz (once per second). Under this circumstance, if, for example, 100 isotopic masses are being analyzed, each isotopic mass will be collected only one hundredth of the entire scan

time. Because of this, the sensitivity of the quadrupole is compromised in multi-element analytical protocols. Degradation in sensitivity may be compensated by increased scan times but, in laser ablation, sample size commonly precludes increasing data acquisition times. Furthermore, in commercial analysis, time constraints are often of paramount importance governing sample throughput.

State-of-the-art ToF LA-ICP-MS Sample Analysis Systems may largely overcome these issues. The principle of operation of a ToF system is significantly different from that of a quadrupole-based system. In a ToF system, the ions are sampled at approximately 20,000 times per second. A specific package of ions is accelerated down a flight path under the influence of an electrical potential. Under these conditions, ions with low mass to charge ratios accelerate faster than heavier ions. Within the electrical field, the ions are refocused and reach the ion detector sequentially, the lightest first and the heaviest, last. The ions from the original ion bundle reach the detector within a 30-microsecond time frame. While they are in the flight path, another ion bundle is accumulated in the accelerator region. Consequently, every 30 microseconds, a fresh batch of ions from the plasma is accelerated down the flight path to the detector. Therefore, instead of sampling a specific isotopic mass every second, it is now possible to sample it every 30 microseconds, or approximately 20,000 times per second, including reset and stabilization times.

This radically improves the sensitivity of the mass spectrometer. However, there are a number of considerations that degrade this sensitivity such that, at present, sensitivities equivalent to conventional quadrupole systems are being achieved. Notwithstanding, equivalent sensitivity to quadrupole systems can now be provided with much smaller sample masses in a much shorter time span. Currently, this is where the ToF Sample Analysis System is superior to quadrupole-based systems in clinical analysis.

In an exemplary operation, the sample is introduced into a laser ablation cell and ablated, using either an Excimer or Frequency Quadrupled Nd-YAG laser, for a period typically not exceeding 30 seconds. Debris from the ablated sample passes down an interface tube, made from Nalgene or suitable other plastic, attached to the torch of an inductively coupled plasma (ICP). The sample debris passes through a zone in this tube, adjacent to the torch, into which independent laser radiation is being passed. A concentric series of dynode detectors measures the photon flux, reflected from the sample debris particles, which facilitates quantitation of particle scattering. Knowing the amount of scattering allows linear correlation to the amount of particles doing the scattering. The Laser scattering device is calibrated using conventional smoke cells.

The level of scattering is a quantitative indication of the amount of debris passing down the tube. This debris contains the sample material (blood) in addition to particles of a pre-coded (with internal standard) carrier matrix. The particles now pass on into the Inductively Coupled Plasma (ICP) where they are ionised and separated using Time of Flight (ToF) segregation. The elemental composition for the sample is established and quantified with reference to the signal obtained form each of the analyte isotopes. Quantitation of the concentration of elements present in the sample and hence the blood, is calculated with reference to the scattering signal from the Laser Interferometer. The amount of sample being analysed is normalized to the signal generation by ionisation of the components in the pre-coded matrix. In this way the amount of material ablated is used to obtain the mass component of the transported material and the elemental signature of the pre-coded matrix facilitates normalization of the response with reference to an ionisation efficiency cross comparison.

The pre-coded matrix may contain a cocktail of elements that are not naturally present in blood, at levels above the detection limit of the technique. These elements typically include one or more (ie. mixture of) Beryllium, Scandium, Zirconium, Niobium, Rhodium, Ruthenium, Indium, Hafnium, Tantalum, Rhenium, Osmium and Iridium. This requires doping of appropriate analytes at levels between 1 and 100µg mL^{-1} to the matrix. The elements are chosen to cover both mass and ionisation potential ranges present in the analytically significant analytes.

Readout from the spectrometer, for reporting purposes, is expressed in concentration units appropriate to clinically accepted protocols. In addition, the readout contains information on the acceptable ranges of analytes in normal healthy individuals and indicate whether the sample under investigation is below, above are in the accepted range.

The methods and devices of the present invention enable the mass screening of a variety of blood or other body fluid samples for a wide range of essential and toxic trace elements. Only a small volume of sample liquid (one or two drops) is required for multiple element analysis. Sample collection of body fluids does not require the use of a hypodermic needle and consequently is essentially non-invasive and considerably safer than existing methods. The sample is collected and stored in an inert matrix without need for addition of preservatives. The sample can be handled and transported safely and easily. The preferred method of analysis, Time of Flight Laser Ablation-Inductively Coupled Plasma-Mass Spectrometry, is very sensitive and can detect and measure trace/ultra trace amounts of an element. The methods described herein are suited to full automation and high throughput screening and analysis of samples. Further, the methods

and devices of the present invention enable multi-element testing at a significantly lower cost than many current single element tests, thus making the economical mass-screening of target populations possible.

A typical procedure of collecting and analyzing a sample is summarized in Figure 5. Of course, manual procedures can also me adopted, as can variations of the proposed exemplary scheme.

Examples of useful areas of application of the methods and devices of the present invention are:

- screening occupationally exposed workers for anomalous levels of a range of toxic metals;
- monitoring environmental exposure of the general population to toxic metals;
- screening populations for trace/ultra trace element deficiencies for preventative medicine
- screening trace/ultra trace element deficiencies, and toxic heavy metal excesses, in bloodstock, general livestock, zoo animals (including animals in endangered species breeding programs), and domestic pets for veterinary medicine; and

monitoring heavy metal pollutants in slaughter animals for meat product quality control in the human food chain.

Although the invention has been described with reference to certain preferred embodiments, variations in keeping with the broad principles and the spirit of the invention are also contemplated as being within its scope.

DATED this 16th Day of April 2002

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Attorney: IVAN A. RAJKOVIC

Fellow Institute of Patent and Trade Mark Attorneys of Australia

of BALDWIN SHELSTON WATERS

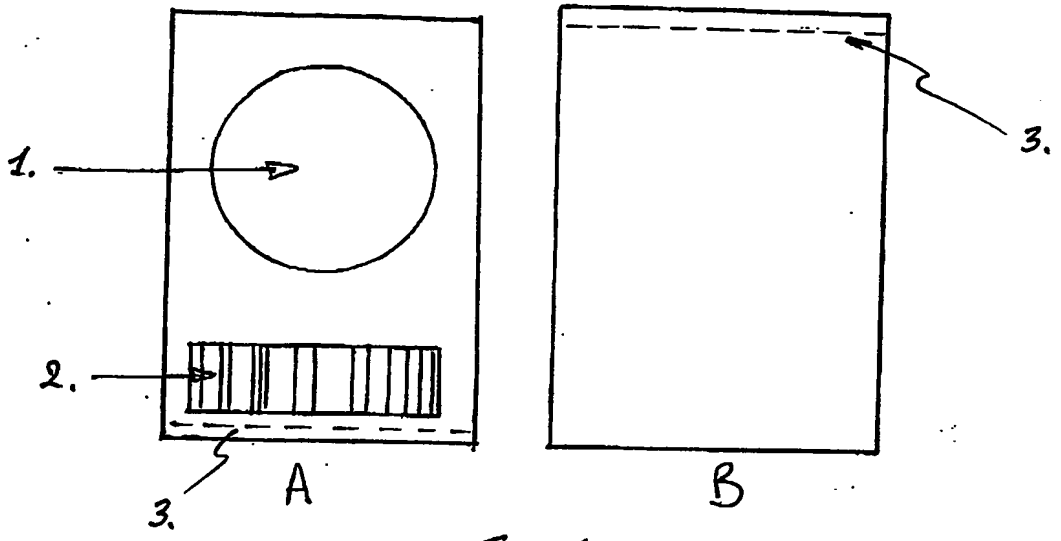

Fig. 1.

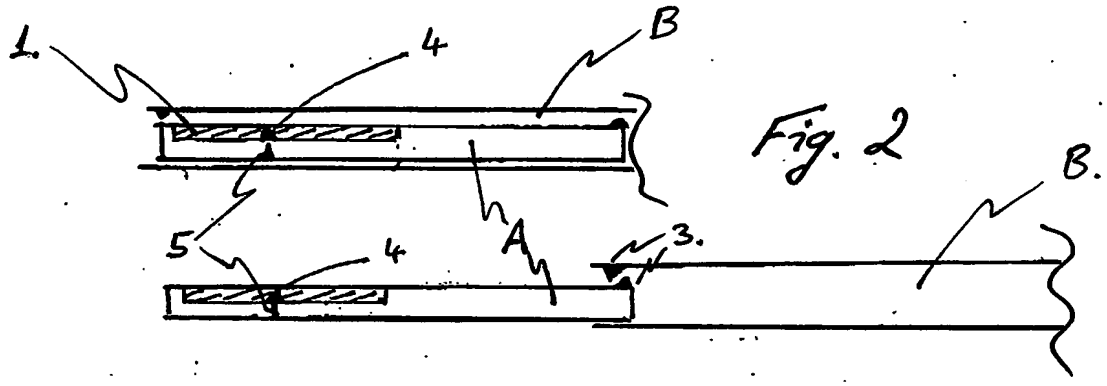

Fig. 2

Fig. 3

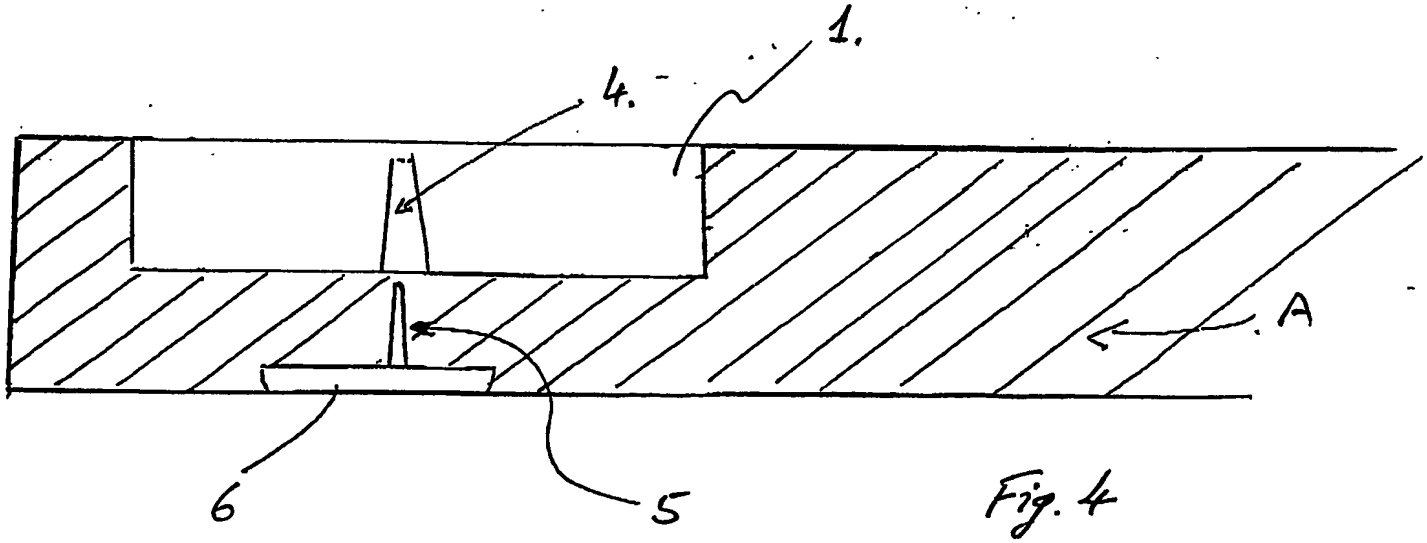

Fig. 4

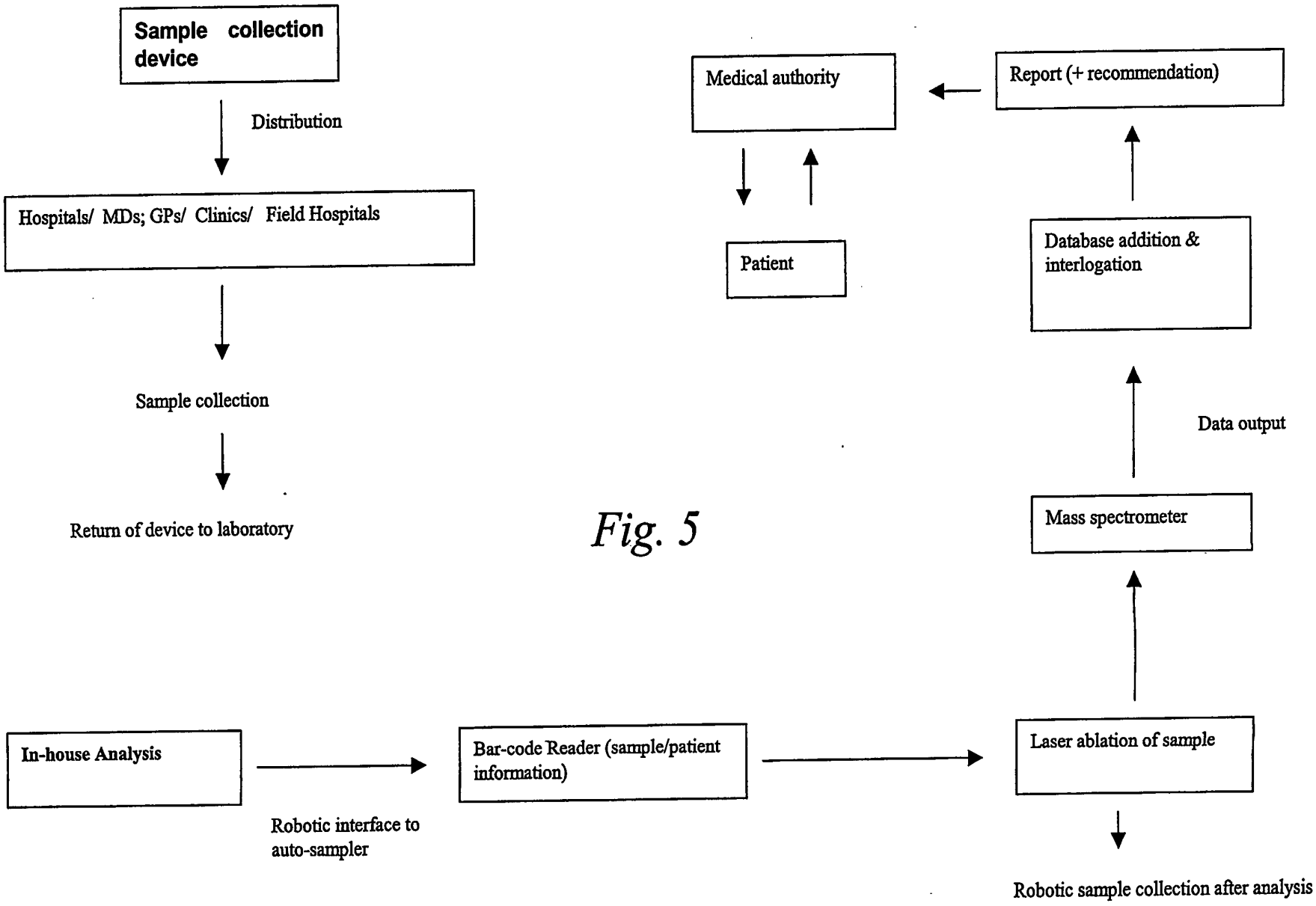
Sample collection device
Distribution
Hospitals/ MDs; GPs/ Clinics/ Field Hospitals
Sample collection
Return of device to laboratory
Medical authority
Patient
Report (+ recommendation)
Database addition & interlogation
Data output
Mass spectrometer
In-house Analysis
Robotic interface to auto-sampler
Bar-code Reader (sample/patient information)
Laser ablation of sample
Robotic sample collection after analysis

Fig. 5